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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/108,673 07/01/98 TENG

C ISIS-3105

EXAMINER

HM22/0226

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ART UNIT

PAPER NUMBER

1636

DATE MAILED:

02/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/108,673

Applicant(s)
Teng et al

Examiner
WILLIAM SANDALS

Group Art Unit
1636



☒ Responsive to communication(s) filed on Dec 20, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 3, 5, 12, 13, 23-27, 32, 33, 35-38, and 40-65 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 3, 5, 12, 13, 23-27, 32, 33, 35-38, and 40-65 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 20 & 24

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 20, 2000 has been entered.

Response to Arguments

2. Arguments and amendments filed on November 9, 2000, Paper No. 18 and on December 20, 2000 in Paper No. 23 have been considered. Arguments which pertain to the rejection of claims 1-40 under 35 USC 112, first paragraph, enablement, have not been found convincing, and the responses to the arguments are contained in the repeated rejection below. Newly entered claims 41-65 have been considered and are rejected as indicated below.

Claim Objections

3. Claim 48 is objected to because of the following informalities: In line 2, the word "polycytidic" appears. This seems to be a misspelling of the word "polycytidylic". Appropriate correction is required.

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Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims 1, 3, 5, 12, 13, 23, 24, 41-43 and 60-65 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-24 of copending Application No. 08/886,829. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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7. Claims 25-27, 32, 33, 35-38 and 40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-47 of copending Application No. 08/886,829. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating, method of investigating of the instant claims 25-40 all require the administration of the claimed pharmaceutical composition to an animal (human), which is a treatment of the animal, making the claimed methods and pharmaceutical compositions patentably indistinct from the claims of the '829 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3, 5, 12, 13, 23-27, 32, 33, 35-38, 40-43 and 60-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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The claims are drawn to pharmaceutical composition, a method of treating and a method of investigating the role of a gene or gene product in an animal having or suspected of having a disease or disorder that is treatable in whole or in part with one or more nucleic acids via the enteral route.

The Specification does not teach one of ordinary skill in the art how to treat or investigate the role of a gene or gene product in an animal (which may be other than a human). Pharmaceutical treatment with nucleic acids is a new and developing art and is highly unpredictable. While the Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a pharmaceutical treatment with nucleic acids, it does not teach one of ordinary skill in the art how to treat nor investigate a role of a gene or gene product with nucleic acids since the practice of the treatment or investigation is highly unpredictable, and would require specific teachings to guide the ordinary skilled artisan how to make and use the claimed invention. As such, specific teachings must be present in the Specification to support any claims to treatment or investigation in an animal with nucleic acid. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

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a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivery via the enteral route of a nucleic acid to an animal and treating the animal with the nucleic acid. Treatment of an animal with a pharmaceutical nucleic acid is a new and developing art, and as such requires detailed teachings on how to make and use such a preparation.

b- The specification teaches the delivery of a nucleic acid via the enteral route to the blood and generally into the internal organs of an animal by cannula delivery of nucleic acids to the small intestine of a rat. There are no teachings of pharmaceutical treatment.

c- The nature of the invention is complex. Treatment of animals with nucleic acids is a new and developing art as taught in Gewirtz et al. (see the entire article). Gewirtz et al. taught the difficulties of therapy with nucleic acids such as antisense oligodeoxynucleotide, stating that there are two major problems which must be overcome. First, the nucleic acid must find its cellular target. Second, it must then find and act on its intracellular target. The specification does not teach one of ordinary skill in the art how to direct the nucleic acid to its cellular target nor how the nucleic acid would then act on its intracellular target.

d- The state of the prior art as taught by Gura (see especially page 575, column 1, second paragraph, and page 576, third paragraph to the end of the article) demonstrates some of the difficulties associated with nucleic acid pharmaceutical therapy, stating "[b]ut the biggest concern is that antisense compounds simply don't work the way researchers once thought they

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did"...."Besides not always working by 'true antisense mechanisms,' the synthetic oligonucleotides have also caused side effects in experimental animals."

e- The state of the art as recited in Stull et al. (see especially pages 476-478) taught that the stability, affinity, efficiency and subcellular distribution of the nucleic acids in the host animal are all areas of uncertainty and need careful study and analysis before any nucleic acid therapeutic modality can be understood and consistently applied. Also, Agrawal et al. taught the delivery of synthetically modified nucleic acids administered to rats via the oral route. However, the nucleic acids had been specifically modified to resist nuclease digestion. Also, no pharmaceutical therapy was demonstrated by Agrawal et al.

f- The teaching of absorption into the blood and internal organs of the nucleic acids in the instant Specification does not demonstrate any targeting of the nucleic acid to a cell or to intracellular targets as recited by Gewirtz et al., nor does the Specification address any of the issues raised by Gura or Stull et al. Therefore, no pharmaceutical effect has been demonstrated.

g- For the reasons stated by Gewirtz et al., Gura, and Stull et al. the unpredictability of pharmaceutical applications of nucleic acids is very high.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

In addition, claim 24 is not enabled because claim 24 recites that an antisense oligonucleotide "modulates" the expression of a cellular adhesion protein or the rate of cellular

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proliferation. The word "modulate" generally means to increase or decrease. An antisense nucleic acid molecule only causes a decrease in expression. Therefore, one of skill in the art would know how to increase expression with an antisense molecule, and a method to increase expression is not taught in the instant specification.

Response to Arguments

10. Arguments set forth in Paper No. 10 assert that any utility for the invention which is enabled provides enablement for all claimed applications of the invention. This is not the case, and pharmaceutical claims which recite nucleic acid must be enabled for pharmaceutical applications of the nucleic acid. As set forth above, the claims are not enabled for a pharmaceutical application of a nucleic acid.

11. Arguments set forth in Paper No. 12 assert that **any utility** (emphasis added) is sufficient to enable the claims to a pharmaceutical composition. As stated above, a pharmaceutical composition has only one utility, namely to treat. The utilities of investigation or studying of a composition do not have a pharmaceutical application. This being the case, the argument is not found convincing.

12. Arguments set forth in Paper No. 23 assert that the utility of the instant pharmaceutical composition derives from the teaching of being able to deliver nucleic acids through the intestinal mucosa. Once again, a pharmaceutical composition has one enabled utility, namely to treat. As stated above, the utility of treating with a nucleic acid (gene therapy) is not enabled.

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13. Arguments set forth in Paper No. 12 assert that antisense technology is enabled by the prior art references provided which demonstrate the use of antisense in experimental systems. These references do not provide a nexus to treatment, and as such are not enabling.

14. It is pointed out that claims 44-59 are enabled, since they are drawn to DNA-containing compositions. Method claims reciting delivery of said compositions via the intestinal mucosa may also be enabled.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

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Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 44-46, 49, 53, 54, 56 and 57 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/05903 (of record).

WO 97/05903 taught (see especially pages 5-8, 14-16 and the claims) a composition comprising two fatty acids (lauric acid and capric acid) and an antisense oligonucleotide. The composition may be water based or propylene glycol based. The composition may have at least 15% bioavailability of the oligonucleotide when administered to a mammal.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

20. Claims 44, 45, 47, 49-51, 53-55, 58 and 59 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,707, 648 (of record).

US Pat No. 5,707, 648 taught (see especially the abstract, the summary, columns 3-8, 12-13 and the claims) a composition comprising two fatty acids, an antisense oligonucleotide and a carrier compound. The composition may be water based (which may be less than 8%) or propylene glycol based. The composition may have at least 15% bioavailability of the nucleic

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acid when administered to a mammal. The composition may contain a bile salt. The antisense oligonucleotide may be chemically modified.

21. Claims 44-59 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 6,092,722.

US Pat No. 6,092,722 taught (see especially columns 9-12, 15, 16, 18, 23-24, 26-27) a composition comprising two fatty acids, an antisense oligonucleotide and a carrier compound which may be dextran sulfate. The composition may be water based or propylene glycol based. The composition may have at least 15% bioavailability of the oligonucleotide when administered to a mammal. The composition may contain a bile salt. The antisense oligonucleotide may be chemically modified and the chemical modification of the antisense oligonucleotide may be a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage or a 2'-methoxyethoxy modification.

Conclusion

22. Certain papers related to this application are *welcomed* to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or

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applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

February 21, 2001


ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER